PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 01 March 2001 (01.03.01)	
International application No.: PCT/AU00/00988	Applicant's or agent's file reference: 100244
International filing date: 18 August 2000 (18.08.00)	Priority date: 19 August 1999 (19.08.99)
Applicant: SHANNON, Anthony, Douglas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

17 November 2000 (17.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
100244		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/AU00/00988	18 August 2000	19 August 1999

Applicant

MINISTER FOR AGRICULTURE, MINISTER FOR LAND AND WATERCONSERVATION FOR AND ON BEHALF OF THE STATE OF NEWSOUTH WALES et al

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention

[X] None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00988

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07K 2/00, 19/00; A61K 39/12, 39/15, 39/44, 47/42; A61P 37/02; C12N 15/12, 15/866

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: Fil WPIDS, MEDLINE, CA, BIOSIS, BIOTECHABS; Keywords: chimeric, fusion, protein?, heat shock protein?, hsp##, immunogen?, antigen?, induce, induct, stimulat, stimulus, vaccine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/29834 (FORDHAM UNIVERSITY) 17 June 1999 Pages 6-7, page 8 line 28-page 9 line 25, page 10 line 6-page 11 line 24, page 13 line 20-37, page 16 line 13-28, page 17 lines 15-24, page 27 lines 7-36, page 32 lines 1-27, page 43 line 35-page 44 line 2; claims 1-6, 14-20, 31, 34-38	1-21
X	WO 99/07860 (STRESSGEN BIOTECHNOLOGIES CORPORATION) 18 February 1999 Page 7 line 20-page 8 line 10, page 11 lines 23-28, page 17 lines 15-18, page 19 lines 3-6, page 20 lines 8-13, page 28; claims 1,2	13-21

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2000	- 9 OCT 2000
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	CHRISTINE BREMERS Telephone No : (02) 6283 2313

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU00/00988

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/23735 (STRESSGEN BIOTECHNOLOGIES CORP.) 4 June 1998 Pages 5-6, pages 10-11, page 12 last paragraph, page 13 second paragraph, page 17, page 25 lines 22-27; claims 1, 3, 4, 13-17	13-21
X	Infection and Immunity Vol 66 No 1 (1998) pages 347-352 (Rico, A I et al) "Characterization of the immunostimulatory properties of Leishmania infantum HSP70 by fusion to the Escherichia coli maltose-binding protein in normal and nu/nu BALB/c mice" Abstract, page 348 column 2 first paragraph, page 349 column 2 second paragraph	13-21
X	European Journal of Immunology Vol 29 No 5 (1999) (Schirmbeck, R et al) "Truncated or chimeric endogenous protein antigens gain immunogenicity for B cells by stress protein-facilitated expression" Abstract, page 1740 column 2 first paragraph, page 1743 column 1 last paragraph to page 1744 column 1 first paragraph, page 1745 column 2 last paragraph to page 1746 column 1 line 2	1, 9, 12
P,X	WO 00/20606 (Reimann H, Schirmbeck R) 13 April 2000 Page 7 lines 23-29, page 9page 13 lines 26-30	13-21
P,X	WO 99/42472 (IGEN INTERNATIONAL, INC.) 26 August 1999 Page 6; claims 1,2, 14, 76 and 77	13-21
P,X	WO 99/42121 (UNIVERSITY OF MIAMI) 26 August 1999 Page 1 lines 9-17, page 9 line 28-page 12 line 10, page 13 lines 1-15, page 17 lines 5-23, page 41 line 1-page 42 line 14, page 50 lines 22-24, page 51 lines 6-14	13-21

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/00988

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	99/42472	AU	24704/99				
WO	99/42121	AU	27731/99				
WO	99/29834	AU	19106/99	EP	1037965	US	5948646
WO	99/07860	AU	64924/98	EP	1002110		
WO	98/23735	AU	51120/98	EP	941315		

END OF ANNEX

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100244:GBC:PK:kv	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00988**	International Filing Date *(day/month/year)* 18 August 2000	Priority Date *(day/month/year)* 19 August 1999

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] C07K 2/00, 19/00; A61K 39/12, 39/15, 39/44. 47/42; A61P 37/02; C12N 15/12, 15/866

Applicant

MINISTER FOR AGRICULTURE, MINISTER FOR LAND AND WATERCONSERVATION FOR AND ON BEHALF OF THE STATE OF NEWSOUTH WALES et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[X]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand 17 November 2000	Date of completion of the report 6 September 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **J.G. HANSON** Telephone No. (02) 6283 2262

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00988

I. Basis of the report

1. With regard to the **elements** of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages **1-70**, as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages **71-73,** received on **28 June 2001** with the letter of **28 June 2001**
- [X] the drawings, pages **1/4, 2/4, 4/4,** as originally filed,
  pages , filed with the demand,
  pages **3/4,** received on **3 September 2001** with the letter of **29 August 2001**
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-20**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1-20**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-20**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

D1 WO 99/29834

D2 WO 99/07860

D3 WO 98/23735

D4 Infection and Immunity

D5 European Journal of Immunology

Novelty and Inventive Step

Claims 1-10 are to a method of producing an immunogenic complex comprising a non-mammalian heat shock protein (hsp) coupled to a heterologous, antigenic peptide, said method comprising subjecting the cell expressing the hsp to a stimulus which causes the induction of a heat-shock response. Claims 11-18 are directed towards a composition comprising a non-mammalian heat shock protein (hsp) coupled to a heterologous, antigenic peptide derived by the method of claims 1-10. Claim 19 is directed towards a pharmaceutical composition of comprising the composition of claims 11-18, and claim 20 is to a method of treatment using the composition of claim 19.

D1 discloses that heat shock proteins form non-covalent complexes with antigenic peptides of cancer cDNA *via* a baculovirus vector and the complexes can elicit specific immunity to the antigenic peptides. However, this document specifically discloses mammalian hsps and therefore novelty of the present claims over D1 is acknowledged. Further, there is no teaching that would suggest to the addressee the use of non-mammalian hsp's. While the heat shock class of proteins is well known for the high degree of structural and functional conservation between species, an inventive step must nevertheless be acknowledged.

D2 discloses a composition where a stress protein is joined non-covalently to a human papilloma virus antigen to induce an immune response in a subject to HPV. Also disclosed is a noncovalent complex between avidin-stress protein fusion protein and biotinylated HPV protein antigen.

D3 discloses stress protein from an insect (Drosophila) chemically conjugated to an influenza virus antigen.

Continued on Supplementary Sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 00/20606	13 April 2000	2 October 1998	2 October 1998
WO 99/42472	26 August 1999	26 January 1999	19 February 1998
WO 99/42121	26 August 1999	19 February 1999	20 February 1998

WO 00/20606 discloses a first polypeptide fused to a second polypeptide and a complex of this fused protein and a chaperone (hsp).

WO 99/42472 discloses a fusion protein of a ubiquitin (hsp) and an epitope-containing segment.

WO 99/42121 discloses a modified hsp introduced into cells containing an antigenic peptide.

These documents are not directly relevant to the present claims as they do not disclose the method of preparing these complexes to which the present claims are directed.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

D4 discloses immunisation with the E. coli MBP-protozoan HSP70 fusion protein and the so-induced powerful cellular response against MBP.

None of D2, D3 or D4 disclose the production of the described complexes *via* the method of claims 1-11. D2 and D3 teach the isolation of the stress proteins prior to complex formation, and none of the documents teach the induction of the stress proteins by stimulating a heat shock response in the same cell that expresses the heterologous antigenic polypeptide.

D5 discloses a heterologous (SV-40) large T antigen as a chimeric protein transfected into mammalian lymphoma cells and expressed as a complex with constitutively expressed hsp73 (ie. expressed in the absence of any specific stimulus).

The present claims differ from D5 in that the cells are non-mammalian and are subjected to stimulus to induce heat s' k response.

Note: Rule 67 lists the subject matter which under Article 34(4)(a)(i) an international preliminary examination is not required to be carried out. At item (iv) it specifies methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, as such matter. However the agreement between WIPO and Australia further qualifies this by excepting from exclusion any subject matter which is examined under national grant procedures. Claim 20 has nonetheless been considered because the identified subject matter does not contravene Australian law.

PCT/AU00/00988
Received 29 August 2001

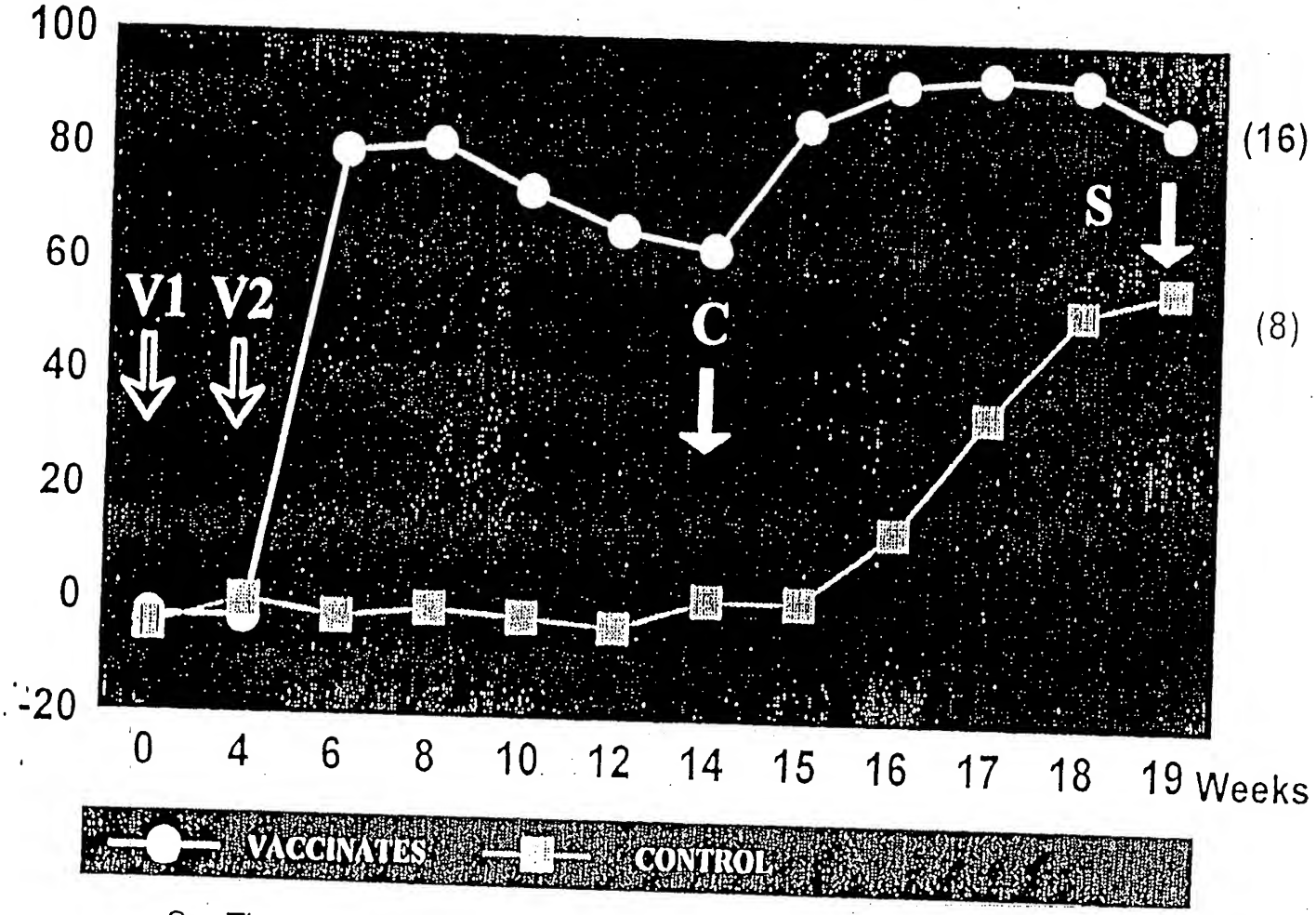
PCT/AU00/00988

AMENDED SHEET
IPEA/AU

Figure 3

EMAI Subunit Vaccine Sheep Trial 458/99

CTB-ELISA Anti-E2 Antibody



S = Time at which the animals were slaughtered and foetuses collected.

The Claims Defining the Invention are as Follows

1. A method of producing an immunogenic complex comprising a non-mammalian heat shock protein (hsp) coupled to a heterologous antigenic polypeptide, which method comprises:

(a) expressing the heterologous antigenic polypeptide in a non-mammalian cell; and

(b) subjected said cell to a stimulus which causes the induction of a heat shock response in said cells; and

(c) recovering heterologous antigenic polypeptide coupled to one or more non-mammalian hsps from said cell or the culture medium.

2. A method according to claim 1 wherein the cell is a non-mammalian eukaryotic cell and the hsp is a non-mammalian eukaryotic hsp.

3. A method according to claim 2 wherein the cell is an insect cell and the hsp is an insect hsp.

4. A method according to any one of the preceding claims wherein the antigenic polypeptide is an antigen of a pathogenic organism, or a fragment or derivative thereof.

5. A method according to claim 4 wherein the pathogenic organism is a virus or a bacterium.

6. A method according to claim 5 wherein the virus is a pestivirus.

7. A method according to claim 6 wherein the virus is bovine viral diarrhoea virus (BVDV).

8. A method according to any one of the preceding claims wherein the antigenic polypeptide is expressed in the cell by the introduction into the cell of a polynucleotide encoding the antigenic polypeptide operably linked

to a regulatory control sequence capable of directing expression of the polypeptide in the cell.

9. A method according to claim 8 wherein the polynucleotide is part of a virus or viral vector.

10. A method according to claim 9 wherein the cell is an insect cell and the virus or viral vector is a baculovirus or baculovirus vector.

11. A composition comprising an immunogenic complex comprising a heat shock protein (hsp) coupled to a heterologous antigenic polypeptide obtained by the method of any one of claims 1 to 10.

12. A composition comprising a heat shock protein (hsp) derived from a non-mammalian eukaryote coupled to a heterologous antigenic polypeptide which composition is capable of inducing an immune response to said antigenic polypeptide in an animal or human, wherein said composition is produced by the method of any of claims 1 to 11.

13. A composition according to claim 12 wherein the hsp is an insect hsp.

14. A composition according to claim 12 or claim 13 wherein the antigenic polypeptide is an antigen of a pathogenic organism, or a fragment or derivative thereof.

15. A composition according to any one of claims 12 to 14 wherein the pathogenic organism is a virus or a bacterium.

16. A composition according to claim 15 wherein the virus is a pestivirus.

17. A composition according to claim 16 wherein the virus is bovine viral diarrhoea virus (BVDV).

18. A composition comprising a pestivirus antigen coupled to a heat shock protein.

19. A pharmaceutical composition comprising an immunogenic amount of a composition according to any one of claims 11 to 18 together with a pharmaceutically acceptable carrier or diluent.

20. A method for inducing immunocompetence in an animal against a pathogen, said method comprising the steps of: administering to an animal a therapeutically effective amount of a pharmaceutical composition according to claim 19.

REPLACED BY ART 34 AMDT

CLAIMS

1. A method of producing an immunogenic complex comprising a heat shock protein (hsp) coupled to a heterologous antigenic polypeptide, which method comprises:

(a) expressing the antigenic polypeptide in a cell which cell has been subjected to a stimulus which causes the induction of a heat shock response in said cells; and

(b) recovering the antigenic polypeptide coupled to one or more hsps from said cell or the culture medium.

2. A method according to claim 1 wherein the cell is a non-mammalian cell and the hsp is a non-mammalian hsp.

3. A method according to claim 2 wherein the cell is a non-mammalian eukaryotic cell and the hsp is a non-mammalian eukaryotic hsp.

4. A method according to claim 3 wherein the cell is an insect cell and the hsp is an insect hsp.

5. A method according to any one of the preceding claims wherein the antigenic polypeptide is an antigen of a pathogenic organism, or a fragment or derivative thereof.

6. A method according to claim 5 wherein the pathogenic organism is a virus or a bacterium.

7. A method according to claim 6 wherein the virus is a pestivirus.

8. A method according to claim 7 wherein the virus is bovine viral diarrhoea virus (BVDV).

9. A method according to any one of the preceding claims wherein the antigenic polypeptide is expressed in the cell by the introduction into the cell of a polynucleotide encoding the antigenic polypeptide operably linked to a regulatory control sequence capable of directing expression of the polypeptide in the cell.

10. A method according to claim 9 wherein the polynucleotide is part of a virus or viral vector.

11. A method according to claim 10 wherein the cell is an insect cell and the virus or viral vector is a baculovirus or baculovirus vector.

12. A composition comprising an immunogenic complex comprising a heat shock protein (hsp) coupled to a heterologous antigenic polypeptide obtained by the method of any one of claims 1 to 11.

13. A composition comprising a heat shock protein (hsp) derived from a non-mammalian eukaryote coupled to a heterologous antigenic polypeptide which composition is capable of inducing an immune response to said antigenic polypeptide in an animal or human.

14. A composition according to claim 13 wherein the hsp is an insect hsp.

15. A composition according to claim 13 or claim 14 wherein the antigenic polypeptide is an antigen of a pathogenic organism, or a fragment or derivative thereof.

16. A composition according to any one of claims 13 to 15 wherein the pathogenic organism is a virus or a bacterium.

17. A composition according to claim 16 wherein the virus is a pestivirus.

18. A composition according to claim 17 wherein the virus is bovine viral diarrhoea virus (BVDV).

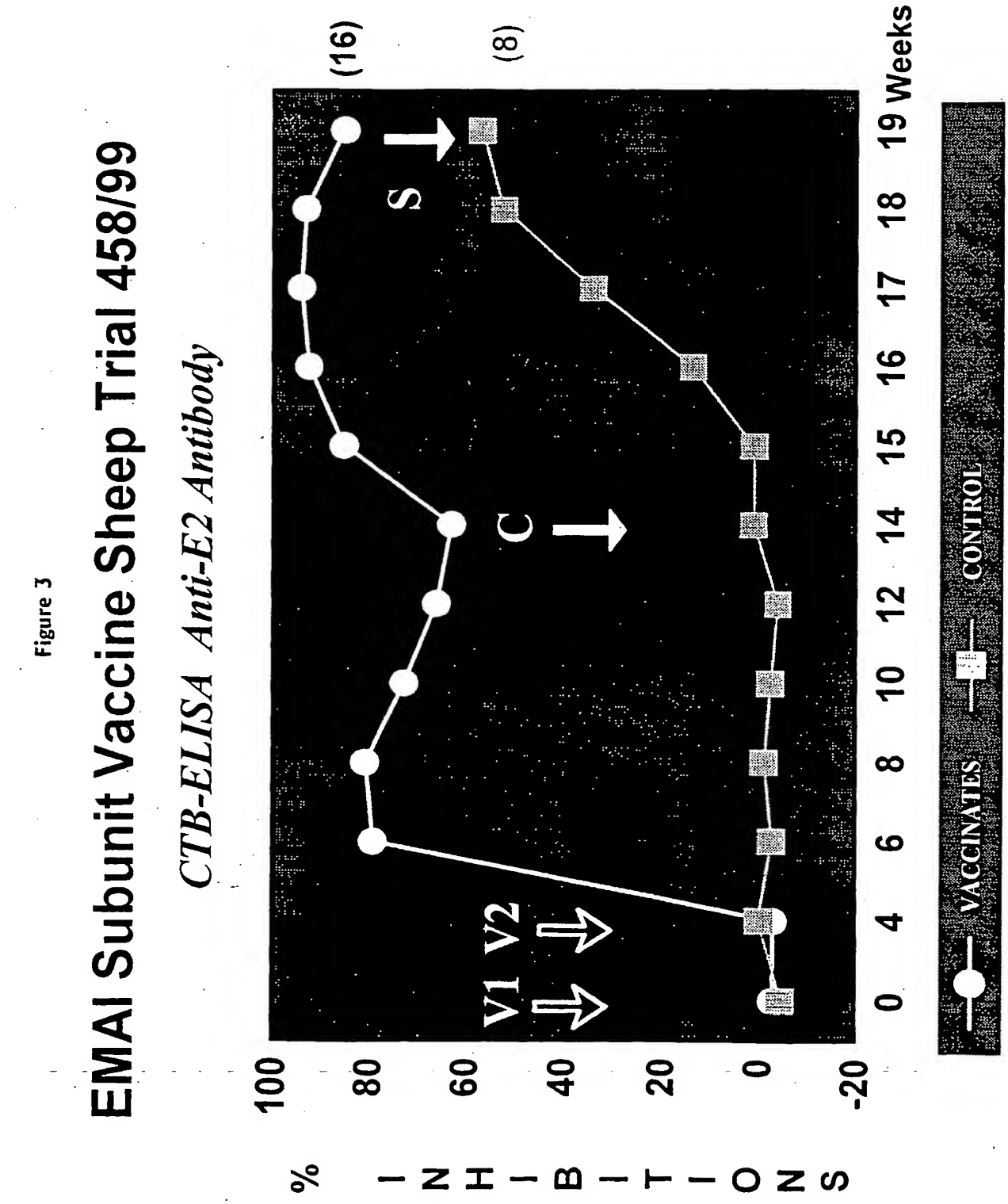
19. A composition comprising a pestivirus antigen coupled to a heat shock protein.

20. A pharmaceutical composition comprising an immunogenic amount of a composition according to any one of claims 12 to 19 together with a pharmaceutically acceptable carrier or diluent.

21. A method for inducing immunocompetence in an animal against a pathogen, said method comprising the steps of: administering to an animal a

therapeutically effective amount of a pharmaceutical composition according to claim 20.

Figure 3


EMAI Subunit Vaccine Sheep Trial 458/99
CTB-ELISA Anti-E2 Antibody
% INHIBITIONS
100
80
60
40
20
0
-20
0
4
6
8
10
12
14
15
16
17
18
19 Weeks
(16)
(8)
S
C
V1
V2
VACCINATES
CONTROL